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2. Patent application number *(The Patent Office will fill in this part)* — 05 FEB 2004 — 0402539.1

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Sinclair Pharmaceuticals Limited
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08803488001

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom (GB)

4. Title of the invention — Xerostomia Treatment, Composition and Method

5. Name of your agent *(if you have one)* — Barker Brettell

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

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Barker Brettell — 4 February 2004

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XEROSTOMIA TREATMENT, COMPOSITION AND METHOD

Field of Invention

The present invention is concerned with the treatment of xerostomia, in particular, with solid pharmaceutical preparations used in the treatment of xerostomia.

Background of the Invention

A reduced salivary secretion may arise or develop with increasing age. Thus, a large number of elderly people have problems with a dry mouth. Some general diseases also give rise to a reduced secretion of saliva, so called hyposalivation. The most prominent one thereof is Sjoegren's syndrom. Furthermore, several generally used medicines, inter alia, anti-hypertensives, anti-ulcer agents and anti-psychotics, have side effects including hyposalivation. Reduced salivary gland function may also accompany or follow a variety of anti-cancer treatments including radiotherapy and chemotherapy. In other words dryness of the mouth, or xerostomia, is a common disease that affects a large number of the population transiently or permanently. The reduced secretion of saliva can cause a variety of subjective symptoms including discomfort of of the tongue, mouth, pharynx and upper esophagus, sensitivity to spicy food and beverages and loss of sleep. Some individuals also have their speech and swallowing affected.

Objectively dryness of the mouth often causes caries and periodontitis, which are difficult to treat since the reduced secretion of saliva results in a more pronounced retention of bacteria in the oral cavity and on the teeth. The resistance of the mucosa against colonization of bacteria is reduced and especially fungal infections are common in connection with individuals with xerostomia. Furthermore, people carrying a plate prosthesis often have great problems with the retention of the prosthesis as well as infection of the mucosa as consequences

of the dryness of the mouth. Other objective signs may include halitosis and recurrent ulcers in the mouth and oropharynx. Natural saliva consists of highly specialized proteins, which are strongly surface-active. They thus form surface films at interfaces of solids and also at soft tissues such as the surfaces of the oral cavity. This film also functions as a lubricant.

US Patent No. 5,260,282 discloses a saliva substitute comprising water-soluble linseed polysaccharides. Said substitute is presented in the form of an aqueous solution. The substitute can be prepared by extracting the polysaccharides from linseed by means of water or a water solution containing inorganic salts.

The types of saliva substitutes, such as those described above, consists of polysaccharides, often chemically modified natural products such as cellulose derivatives, for example carboxymethyl cellulose. They provide viscosity, but only very limited surface activity. The extraction procedure used to prepare linseed extract gives beside polysaccharides a considerable amount of proteins. These proteins are also quite surface active as seen by adsorption measurements. Linseed extract can emulsify oil and this is also a desired property of a saliva substitute, since oils in the food must be dispersed into water phase

Summary of Invention

In accordance with the present invention, there is provided a solid pharmaceutical composition, characterised in that it comprises a water soluble linseed extract and a pharmaceutically acceptable excipient.

There is further provided a spray dried composition, characterised in that it comprises a water soluble linseed extract.

According to a further aspect of the present invention there is provided a freeze dried composition, characterised in that it comprises a water soluble linseed extract.

In accordance with a further aspect of the present invention, there is provided a process for the production of a composition comprising a water soluble linseed extract, comprising spray drying or freeze drying a aqueous solution or dispersion of said water soluble linseed extract.

In accordance with a further aspect of the present invention, there is provided an aqueous pharmaceutical preparation obtainable by dissolving or dispersing a solid composition as defined above in a solvent comprising water.

In a further aspect of the present invention, there is provided a method of treating xerostomia comprising the administration of pharmaceutical composition or an aqueous pharmaceutical preparation as defined above to a patient.

The salivary glands of the mouth normally produce around 1-1.5 litres of saliva per 24 hours, and it must be considered unrealistic to utilize a saliva substitute that has to be taken in such a volume per 24 hours. Thus, the present invention provides an alternative to liquid saliva substitutes, while providing a number of advantageous physical properties discussed below.

Linseed contains polysaccharides and proteins exhibiting physical properties, which are similar to those of mixed saliva. For patients with reduced saliva production, who comprise the majority of patients with xerostomia, a solid dosage form, for example a tablet, does not at first sight make sense. However, a dry formulation is more convenient because it can be used discreetly, is easily carried and can have slow release characteristics and greater control on the duration of action. It may further provide benefits of higher stability, easier handling, easier transportation and lower manufacturing and packaging costs.

It has now been found that the process of drying the linseed extract has a surprising effect on the physical properties of the linseed extract. A surprising increase in adsorption to surfaces, especially to tissue, in particular mucosal tissue, is observed. Without wishing to be bound by theory, it is postulated that these changes in physical properties are attributable to changes in the structure of the proteins associated with the linseed extract. Such changes have particular advantages in treatment of xerostomia as an increased adsorption leads to longer residence times on tissue and smaller dosage requirements. Additionally, a resultant solution has improved film-forming properties and gives a much improved mouth feel. This latter advantage is attributed to the solution having a similar viscosity and lubricity to natural saliva.

As discussed above, it is known that the mixture of proteins and polysaccharides present in linseed extract possess a very unusual combination of rheological and surface-chemical properties, which make them extremely suitable for the application described in the present invention. Prior art teachings suggest that the linseed extract should be applied to the patient in the form of an aqueous composition, effectively a saliva substitute. The present invention teaches quite the contrary. The present invention teaches the administration of a solid composition to the patient. This is contrary to what one would expect when treating patients suffering from xerostomia.

Such solid preparations provide a convenient metered dose, a discrete packaging and form of administration to the patient and substantially less packaging then an aqueous product.

Preferably the solid compositions of the present invention are directly administrable to a patient. That is to say that the solid formulation may be used in the treatment, rather than have to be made up into a solution. The solid

compositions of the present invention find particular utility in patients suffering from mild to moderate xerostomia.

The linseed extract is of the type that is obtainable by a simple extraction in water of said polysaccharides and proteins directly from linseed as described in patent no. US 5,260,282, which is incorporated herein by reference. Of course, any extraction method may be employed, for example extraction with an organic solvent alone or with water, a supercritical fluid or a mixture of the above. Where a mixture of an organic solvent and water is used, preferably a protic solvent such as ethanol is utilised.

One advantage of using a supercritical fluid to extract the polysaccharide and protein fraction from the linseed is that it is extremely easy to remove the solvent from the extract, thus reducing the process steps in order to arrive at a solid product.

The linseed extract used in the present invention may be obtained by simple dissolution or extraction from linseed in water at ambient temperature, however elevated temperatures and/or pressures may be utilised in the extraction.

In a particularly preferred embodiment, the solid compositions of the present invention are produced by spray drying or freeze drying solutions, preferably aqueous solutions comprising the linseed extract. Conventional spray drying and freeze drying techniques may be employed. Spray drying and freeze drying techniques have been shown to provide advantageous processing features which have the effect of altering the structure of the proteins associated with the linseed extract. Spray drying is especially preferred as this leads to the most marked change in the physical properties of the linseed extract, for example the adsorption characteristics.

Preferably, spray drying takes place at a temperature of greater than 110°C, preferably greater than 135°C, more preferably greater than 150°C, most preferably greater than 170°C, for example, about 180°C.

The adsorption of an aqueous solution, as measured using ellipsometry on a silica substrate, formed by dissolution of the above mentioned solid composition preferably has an adsorption in the range of 0.5-5 mg/m^2, more preferably 1.2-4 mg/m^2, more preferably 1.5-3 mg/m^2, most preferably in the range of 1.75-2.5 mg/m^2. This adsorption is preferably measured after a residence time on the silica of between 100 and 3000 seconds, more preferably 500-2500 seconds, most preferably between 1000 and 2000 seconds.

Preferably the solid composition of the present invention is substantially free of water. The solid composition has preferably less than 10% water by weight of composition, more preferably less than 5% water by weight, more preferably less than 2% water by weight, most preferably less than 1% water by weight.

A number of additives may be advantageously included in the composition of the present invention.

In a particularly preferred embodiment a sialogogue is present in the solid composition. Preferred sialogogues include pharmaceutically acceptable organic acids such as citric acid, malic acid, ascorbic acid, fumaric acid and the like. Malic acid is a particularly preferred sialogogue.

In a particularly preferred embodiment, a lubricious polymer is included in the composition. This aids is the disintegration of the solid composition and in dispersing the composition around the oral cavity. Preferred polymers are selected from alkylene oxide polymers and interpolymers and derivatives thereof where the terminal hydroxyl groups have been modified by esterification, etherification, etc. These are exemplified by the compounds prepared through

polymerization of ethylene oxide or propylene oxide and the alkyl and aryl ethers of these polyoxyalkylene polymers. Casein fractions can also provide this function.

The present invention may also be used to deliver a wide variety of physiologically active compounds and drugs to a patient. As used herein, the term "drug" refers to chemical or biological molecules providing a therapeutic, diagnostic, or prophylactic effect in vivo. The present invention has proved to be particularly useful where it is not possible, or is difficult to produce and maintain a stable aqueous solution incorporating a drug or physiologically active compound. The solid formulations according to the present invention have proved to be more stable, have longer shelf life etc.

Drugs contemplated for use in the compositions described herein include the following categories and examples of drugs and alternative forms of these drugs such as alternative salt forms, free acid forms, free base forms, and hydrates:

Analgesics/antipyretics, for example aspirin, acetaminophen, ibuprofen, naproxen sodium, buprenorphine, propoxyphene hydrochloride, propoxyphene napsylate, meperidine hydrochloride, hydromorphone hydrochloride, morphine, oxycodone, codeine, dihydrocodeine bitartrate, pentazocine, hydrocodone bitartrate, levorphanol, diflunisal, trolamine salicylate, nalbuphine hydrochloride, mefenamic acid, butorphanol, choline salicylate, butalbital, phenyltoloxamine citrate, diphenhydramine citrate, methotrimeprazine, cinnamedrine hydrochloride, and meprobamate;

Antifungal agents, for example, griseofulvin, ketoconazole, itraconizole, amphotericin B, nystatin, and candicidin;

Anti-inflammatories, for example, (non-steroidal) indomethacin, ketoprofen, flurbiprofen, naproxen, ibuprofen, ramifenazone, piroxicam, (steroidal)

cortisone, dexamethasone, fluazacort, celecoxib, rofecoxib, hydrocortisone, prednisolone, and prednisone;

Antibacterial agents, for example, amikacin sulfate, aztreonam, chloramphenicol, chloramphenicol palirtate, ciprofloxacin, clindamycin, clindamycin palmitate, clindamycin phosphate, metronidazole, metronidazole hydrochloride, gentamicin sulfate, lincomycin hydrochloride, tobramycin sulfate, vancomycin hydrochloride, polymyxin B sulfate, colistimethate sodium, and colistin sulfate;

Antiviral agents, for example, interferon alpha, beta or gamma, zidovudine, amantadine hydrochloride, ribavirin, and acyclovir;

Antimicrobials, for example, cephalosporins such as cefazolin sodium, cephradine, cefaclor, cephapirin sodium, ceftizoxime sodium, cefoperazone sodium, cefotetan disodium, cefuroxime e azotil, cefotaxime sodium, cefadroxil monohydrate, cephalexin, cephalothin sodium, cephalexin hydrochloride monohydrate, cefamandole nafate, cefoxitin sodium, cefonicid sodium, ceforanide, ceftriaxone sodium, ceftazidime, cefadroxil, cephradine, and cefuroxime sodium; penicillins such as ampicillin, amoxicillin, penicillin G benzathine, cyclacillin, ampicillin sodium, penicillin G potassium, penicillin V potassium, piperacillin sodium, oxacillin sodium, bacampicillin hydrochloride, cloxacillin sodium, ticarcillin disodium, azlocillin sodium, carbenicillin indanyl sodium, penicillin G procaine, methicillin sodium, and nafcillin sodium; erythromycins such as erythromycin ethylsuccinate, erythromycin, erythromycin estolate, erythromycin lactobionate, erythromycin stearate, and erythromycin ethylsuccinate; and tetracyclines such as tetracycline hydrochloride, doxycycline hyclate, and minocycline hydrochloride, azithromycin, clarithromycin; and,

Antiulcer agents, for example, famotidine, cimetidine, and ranitidine hydrochloride.

Suitable routes of administration may, for example, include oral, rectal, transmucosal administration, preferably oral administration.

A product of the present invention may be administered to a patient in need in pharmaceutical compositions where it is mixed with suitable carriers or excipient(s) at doses to treat or ameliorate xerostomia. Such a composition may also contain diluents, fillers, salts, buffers, stabilizers, solubilizers, binders, disintegrators, thickeners and other materials known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s).

Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. These pharmaceutical compositions may be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating or entrapping processes. Most preferably, spray drying or freeze drying are used to prepare a pharmaceutical preparation which may then undergo further processing to produce, for example, a tablet or the like.

When a therapeutically effective amount of the composition of the present invention is administered orally, the composition will preferably be in the form of a tablet, capsule or powder. For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules and the like, for oral administration to a patient to be treated.

Preferred excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, xylitol, galactitol, isomaltose or sorbitol and mixtures thereof; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). Preferably, non-cariogenic excipients are used.

Preferred disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, starch, carboxymethylcellulose, carragenans, carboxymethylcellulose calcium, croscarmellose sodium and carboxymethylstarch sodium.

Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterise different combinations of doses.

Binder is preferably selected from the group consisting of crystalline cellulose, sucrose, D-mannitol, dextrin, hydroxypropylcellulose, hydroxypropylmethylcellulose, and polyvinylpyrrolidone.

Preferred thickeners or viscosity builders include natural gums, cellulose derivatives, and acrylic polymers.

Preferred examples of the solubilizer are polyethylene glycol, polypropylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate and sodium citrate.

Preferred buffers includes phosphate, acetate, carbonate, citrate and other buffer solutions.

Preferred preservatives includes p-hydroxybenzoic esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, and sorbic acid. Preferred examples of the antioxidant are sulfites and ascorbic acid.

Where necessary, such other additives as preservatives, antioxidants, colouring agents, sweeteners and the like can be incorporated.

The compositions of the present invention may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration.

Tablets, powders and granules may be manufactured by adding an excipient, a disintegrator, a binder, a lubricant, etc. and compression-molding the mixture.

Quick dissolve tablets may be prepared, for example, without limitation, by mixing the formulation with agents such as sugars and cellulose derivatives, which promote dissolution or disintegration of the resultant tablet after oral administration, usually within 30 seconds.

Chewable tablets, for example, may be prepared by mixing the formulations with excipients designed to form a relatively soft, flavored, tablet dosage form that is intended to be chewed rather than swallowed. Conventional tablet machinery and procedures, that is both direct compression and granulation, i.e., or slugging, before compression, can be utilized. Those individuals involved in pharmaceutical solid dosage form production are well versed in the processes and the machinery used as the chewable dosage form is a very common dosage form in the pharmaceutical industry.

Compressed tablets, for example, may be prepared by mixing the formulation

with excipients intended to add binding qualities to disintegration qualities. The mixture is either directly compressed or granulated then compressed using methods and machinery quite well known to those in the industry. The resultant compressed tablet dosage units are then packaged according to market need, i.e., unit dose, rolls, bulk bottles, blister packs, etc.

Brief Description of the Drawings

Figure 1 Shows the adsorption of redissolved linseed extract formulations (10%) on silica. Rinsing was started at 1800 seconds for the mixture.

Detailed Description of the Invention

Materials

A liquid linseed extract formulation, made in accordance with the process described in US Patent No. 5,260,282, was used as starting material and was provided by Biosurface Pharma AB.

Ellipsometry

Ideally film formation should be measured on a soft tissue such as the inside of a lip. There exists, however, no method that can do this with accuracy. Ellipsometry is very accurate in order to measure surface load, but requires an optically reflecting surface. Silica surfaces, used in the present experiments, have been shown to accumulate salivary material in a way similar to hydroxyapatite, which is the major inorganic component in tooth enamel.

Ellipsometry is an optical method to measure the changes in polarisation of light upon reflection at a surface (Azzam R M A, Bashara N M, "Ellipsometry and polarised light", North-Holland Amsterdam, 1977). The instrument used was a

Rudolph thin film ellipsometer, type 436 (Rudolph Research, Fairfield, N. J.), equipped with a xenon lamp filtered to 4015 Å. To determine the ellipsometric angles, Δ and ψ for the bare substrate, the position of the intensity minimum was established. From the changes in Δ and ψ, compared to the clean substrate, the thickness and refractive index of a thin film can be calculated according to McCrackin et al. (McCrackin F L, Passaglia E, Stromberg R R, Steinberg H L, J. Res. Nat. Bur. Stand. (1963); A67:363). The adsorbed amount was calculated according to Cuypers et al. (Cuypers P A, Corsel J W, Janssen M P, Kop J M M, Hermens W T, Hemker H C, J. Biol. Chem. (1983); 258:2426) using values for the ratio between molar weight and molar refractivity and for the partial specific volume of 4.1 g/ml and 0.75 ml/g, respectively. Stock solutions were added to milli-Q water, unless otherwise stated, to give 5 ml solution in the ellipsometer cuvette with a protein concentration of 10%. Hydrophilic silica surfaces with an oxide layer of 300 to 350 Å, obtained by thermal oxidation of silicon test slides (p-type, boron doped, resistivity 1-20 $\Omega \cdot$cm), were used as substrates.

The hydrophilic silica surfaces were cleaned according to the following procedure: The surfaces were immersed for 5 min at 80°C first in $NH_4:H_2O_2:H_2O$ (1:1:5) (v/v/v) and then in $HCl:H_2O_2:H_2O$ (1:1:5) (v/v/v) with subsequent rinsing in water and after the last step rinsing in ethanol. The cleaned surfaces were stored in ethanol. Immediately prior to use the surface was rinsed in ethanol and water and after drying in the flow of dry nitrogen, plasma cleaned in low pressure residual air, using a radio frequency glow discharge unit (Harrick PDC 3XG, Harrick Scientific Corp., Ossining, New York). As was obvious from their water wettability the surfaces were hydrophilic.

Spray-drying

Linseed extract was spray dried in a conventional spray-dryer. The dimensions of the drying chamber are 0.5 x 0.15 m^2. The spray dryer operates co-currently and has a spray-nozzle with an orifice 1 mm in diameter. Inlet gas temperature

was 180°C. Outlet gas temperature was kept at 80°C. Liquid feed to the dryer was 5 ml/min. The flow of drying air was 0.8 m^3/min. Powder was collected in a cyclone at the outlet. Powders were stored at room temperature in closed containers within a desiccator.

Freeze-drying

Freeze-drying was performed in a laboratory freeze-drier Lyovac GT 2 (Steris GmbH, Hurth, Germany). The samples were frozen separately at –80 °C and transferred to the freeze-drier in frozen state. Drying was performed at 0.1 mbar for 70 hours.

Examples

Test of spray dried and freeze dried linseed extract powders:

Adsorption properties of the aqueous redissolved formulations were measured by ellipsometry (Figure 1) and compared to the same characteristics of a linseed extract prepared according to the examples of US 5,260,282.

The adsorption behaviour of linseed extract was affected slightly by freeze drying, whereas the spray-dried product gave a significantly higher adsorbed amount. The adsorption effects observed on the linseed extract of the present invention by drying are quite unexpected. It appears that the protein fraction in linseed extract plays a significant role.

Furthermore, the film forming properties of the spray-dried product were significantly better than both untreated and freeze-dried linseed extracts, as indicated by higher adsorbed amounts on silica. This unexpected behaviour is

likely due to changes in conformation and/or association of proteins and shows that spray drying gives significant advantages.

Tablet formulations of linseed extract powders:

An example of a tablet composition according to the present invention was prepared by mixing the ingredients presented in Table 1. The tablets are referred to as Salinum tablets. Salinum is the trade name applied to the linseed extract utilised in the present invention.

Table 1. Example of composition of Salinum tablets

Ingredient	**Amount (percent w/w)**
Salinum dry substance	3.3
Isomalt	53.1
Xylitol	37.4
malic acid	4.7
magnesium stearate	1.5

Typical laboratory batch productions of Salinum tablets were started with dry Salinum powder and grinding it at low temperature in a mortar together with xylitol. This was followed by mixing with isomalt and malic acid in a turbula mixer for 10 minutes, and finally by addition of magnesium stearate including further 2 minutes of turbula mixing. The granulate was then transferred to an eccentric tablet press (Diaf TM-20).

Salinum protects and lubricates hard and soft surfaces of the oral cavity due to its composition of polysaccharides and proteins. The function of these components is to increase viscosity and provide film formation through surface activity, respectively. An important property of Salinum is its ability to form such films on different types of surfaces, which is important for its effectiveness. This also contributes to the comparatively long duration of residence of Salinum.

Claims

1. A solid pharmaceutical composition, characterised in that it comprises a water soluble linseed extract and a pharmaceutically acceptable excipient.

2. A spray dried composition, characterised in that it comprises a water soluble linseed extract.

3. A freeze dried composition, characterised in that it comprises a water soluble or dispersible linseed extract.

4. A composition according to any of claims 1 to 3, for use in the treatment of xerostomia.

5. A composition according to any preceding claim, wherein the composition preferably comprises less than 10% water by weight, more preferably less than 5% water by weight, more preferably less than 2% water by weight, most preferably less than 1% water by weight.

6. A composition according to any preceding claim, further comprising a sialogogue, preferably selected from organic acids, most preferably from citric acid, malic acid, ascorbic acid and fumaric acid.

7. A composition according to any preceding claim, further comprising a lubricious polymer, preferably selected from the group consisting of alkylene oxide polymers, caseins, interpolymers and derivatives thereof where the terminal hydroxyl groups have been modified by esterification, or etherification.

8. A composition according to any preceding claim, further comprising one or more physiologically active compounds or drugs.

9. A composition according to any preceding claim, further comprising a compound selected from the group consisting of diluents, fillers, salts, buffers, stabilizers, solubilizers, binders, disintegrators and thickeners.

10. A composition according to any preceding claim, wherein the water soluble linseed extract is spray dried prior to or during formulation into a pharmaceutical preparation.

11. A composition according to any preceding claim, wherein the water soluble linseed extract is freeze dried prior to or during formulation into a pharmaceutical preparation.

12. A composition according to any preceding claim, presented as a tablet, capsule or a powder.

13. A pack or dispenser device comprising one or more unit dosage forms of a composition according to any preceding claim.

14. An aqueous composition obtainable by dissolution of a composition according to any preceding claim, in a solvent comprising water.

15. A process for the production of a composition comprising a water soluble linseed extract, comprising spray drying or freeze drying a aqueous solution or dispersion of said water soluble linseed extract.

16. A process according to claim 15, wherein the composition further comprises a pharmaceutically acceptable excipient.

17. A process according to claim 15 or claim 16, wherein the composition further comprises one or more physiologically active compounds or drugs.

18. A process according to any of claims 15 to 17, wherein the composition further comprises a compound selected from the group consisting of diluents, fillers, salts, buffers, stabilizers, solubilizers, binders, disintegrators and thickeners.

19. A method of treating xerostomia comprising the administration to a patient of a pharmaceutical composition or an aqueous pharmaceutical preparation according to any of claims 1 to 12 and 14 to a patient.

20. A method according to claim 19, wherein the composition is administered orally.

21. Use of a solid composition according to any of claims 1 to 12 and 14, for use in the preparation of a pharmaceutical composition, for treatment of xerostomia.

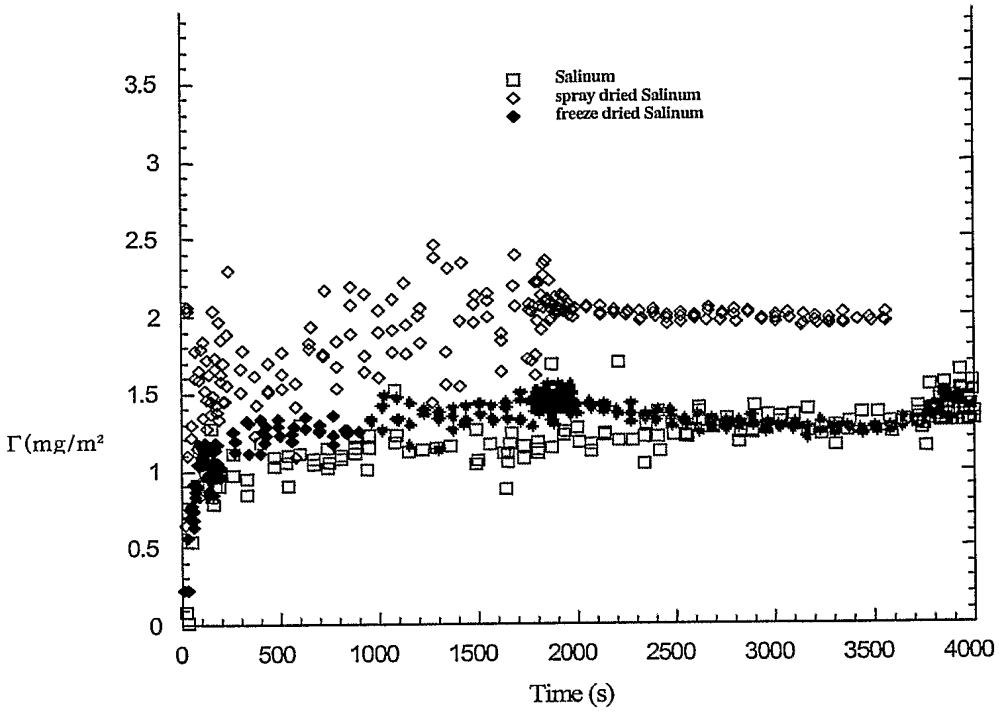
Salinum
spray dried Salinum
freeze dried Salinum
Γ(mg/m²
3.5
3
2.5
2
1.5
1
0.5
0
0
500
1000
1500
2000
2500
3000
3500
4000
Time (s)

Figure 1.